DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

NOV 15 2000

Lifecore Biomedical, Inc.
c/o Karen M. Becker, Ph.D.
The Weinberg Group, Inc.
1220 Nineteenth St., NW, Suite 300
Washington, DC 20036-2400

Re: P990015
Intergel® Adhesion Prevention Solution
Filed: March 8, 1999
Amended: May 12, August 25, September 10, 13, 21, and 29, December 15 and 16, 1999, February 4, April 11, June 2, and September 12, 2000

Dear Dr. Becker:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA).

The General and Plastic Surgery Devices Panel recommended to CDRH at the January 12, 2000 panel meeting that the PMA be considered not approvable. After we informed you that FDA also believed that the PMA was not approvable, you requested an opportunity to provide an additional analysis in an attempt to support a revised indication for use. This retrospective analysis was submitted on June 2, 2000. In a letter dated September 8, 2000, the CEO of Lifecore, Dr. James W. Brackey, requested that Dr. David Feigal resolve some issues related to this PMA. Dr. Feigal suggested that the sponsor meet with management in the Office of Device Evaluation (ODE). He advised that, if necessary, other dispute resolution options could still be considered subsequently. ODE met with representatives of the firm on October 27, 2000, at which time we discussed our initial review of the analysis. A further review of the data and outstanding issues related to this PMA was then conducted following the meeting.

We regret to inform you that CDRH has determined that your application is not approvable based on the requirements of 21 CFR 814.44(f), which also requires FDA, where practical, to identify measures necessary to make the PMA approvable. The reasons for the not approvable finding are as follows:

Although the results of clinical testing with this device may appear to be encouraging, there is not sufficient information directly relating the performance of the device to the proposed indication for use to demonstrate reasonable assurance of safety and effectiveness. The results of your pivotal clinical study, performed in the U.S. and in Europe, were presented at the panel meeting on January 12, 2000. In the panel's opinion, as stated above, the data did not show a clinically significant benefit for the Intergel® Solution-treated group when compared to the lactated Ringer's solution control group.

The retrospective analysis submitted on June 2, 2000, used observations originally obtained as part of a modified AFS (mAFS) scoring system. These were restructured into a different scale (AFS scores) to assess a more restricted endpoint – consideration of adnexal adhesions. There is little experience in the clinical literature correlating the mAFS score with clinical outcomes. When the data are then reorganized into a different scale for later analysis, correlation of the results to any clinically meaningful outcome becomes difficult.

AFS score data and the associated "shift" tables examined the proportions of patients with no adhesions, minimal/mild adhesions and moderate/severe adhesions at baseline and at second look in the Intergel® Solution and Control groups. As stated on page 6 of Section III of your amendment: "The primary efficacy analysis was based on AFS adhesion score, providing for consideration of data for each patient by score and category. In the effectiveness analysis, the failure rate in the Intergel® Solution subjects was compared to the failure rate in the control group. A moderate or severe AFS adhesion category at second-look was considered a treatment failure in this study; i.e., an AFS score of moderate (11-20) or severe (21-32) at second-look laparoscopy was a treatment failure." You conclude that the Intergel® Solution group had a 5-fold lower number of moderate or severe adhesions at second-look compared to control group and that this effect was clinically significant. This analysis reported a statistical benefit that was driven by the baseline moderate/severe patients, accounting for approximately 10% of the study population. These moderate/severe patients were not patients that the original study was designed to evaluate.

The panel noted in their January 12, 2000, meeting that the patients in the treatment group exhibited a higher infection rate than that observed for the control patients. Your June 2, 2000, amendment included a reevaluation of the clinical infection data and some additional animal infection data. The animal study showed that Intergel® did not contribute to deaths or to abscess formation in rats. However, the reevaluation of the clinical infection data still showed a higher level of infections in the Intergel® patients compared to the patients treated with lactated Ringer's solution. You addressed this issue in your presentation to FDA on October 27, 2000, and answered many of our remaining questions. After taking the nature of the infection reports into account, however, there may still be an increase in infection rate. Although small, this increase might be clinically significant in a population concerned about infertility. There is not sufficient information available to make a final determination of safety.

Accordingly, to place your PMA in approvable form, you must amend your PMA to include the results of clinical studies demonstrating reasonable assurance of medically significant effectiveness and safety following pelvic gynecologic surgery. It is important that you carefully select the scale to be used for recording data and calculating results. You may wish to consider performing a study on patients with moderate/severe baseline adhesions. FDA would be pleased to meet with you to discuss appropriate study designs and to review a proposed protocol.

The deficiencies identified above represent the issues that we believe need to be resolved before our review of your PMA application can be completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at:
http://www.fda.gov/cdrh/modact/leastburdensome.html

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided by 21 CFR 814.44(f), you may amend your PMA as requested above, withdraw the PMA, or consider this letter to be a denial of approval of the PMA under 21 CFR 814.45. If you consider it to be a denial, you may request administrative review, either through a formal evidentiary public hearing (21 CFR Part 12) or by an independent advisory committee, the newly established Medical Devices Dispute Resolution Panel (21 CFR 10.75(b)(2), under section 515(d)(4) and 515(g) of the Federal Food, Drug and Cosmetic Act. Either request for review must be submitted within 30 days of your receipt of this letter . You may wish to discuss these appeal options, and any others that may be available to you, with the CDRH Ombudsman, Les Weinstein. As you know, Mr. Weinstein attended our October 27 meeting. He can be reached at 301-443-6220 ext. 119.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA number and will be subject to the requirements of 21 CFR 814.20.

You may amend the PMA to provide the above requested information (6 copies), voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information or request an extension.

The required copies of the amended PMA should include the FDA reference number to facilitate processing for this PMA and should be submitted to the following address:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd
Rockville, Maryland 20850

If you have any questions concerning this not approvable letter, please contact me at 301-594-2022 or Dr. David Krause, at (301) 594-3090, extension 141.

Sincerely yours,

Kimber C. Richter

Kimber C. Richter, M.D.
Deputy Director for Clinical and
Review Policy
Office of Device Evaluation
Center for Devices and
Radiological Health